

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of

Jan Yngvar PIENE et al.

**ATTN: BOX PATENT APPLICATION**

Application No: 09/831,553

Filed: May 11, 2001

Title: PROCESS FOR PREPARING ORAL CALCIUM COMPOSITIONS

**CLAIM FOR PRIORITY UNDER 35 U.S.C. §119**

Commissioner of Patents  
Washington, D.C. 20231

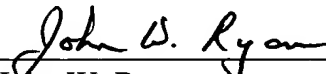
Sir:

Under the provisions of 35 U.S.C. §119, Applicant claims the benefit of the filing date of Great Britain application no. 9825033.5 filed November 13, 1998 for this application, and enclose a certified copy of said Great Britain application in support of the claim for priority.

If there are any fees due or overpaid in connection with this submission, please charge or credit any overpayments to Deposit Account No. 50-1656.

Respectfully submitted,  
WILMER CUTLER & PICKERING

Dated: November 5, 2001

  
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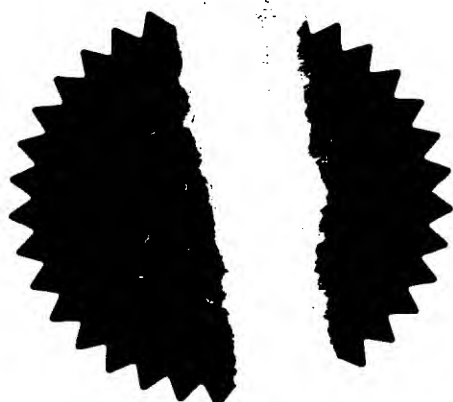
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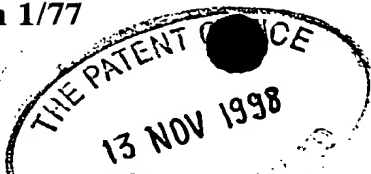
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|--|--|---|--|
| 1. Your reference  | 44.67810/000   |   |  |
| 2. Patent application number<br>(The Patent Office will fill in this part)   | 13 NOV 1998  | 9825033.5                                       |  |
| 3. Full name, address and postcode of the<br>or of each applicant (underline all surnames)   | Nycomed Pharma AS<br>Sandakerveien 100C<br>N-0401 Oslo<br>Norway |   |  |
| Patents ADP number (if you know it)  |  |   |  |
| If the applicant is a corporate body, give<br>country/state of incorporation   | Norway   | 6261515000                                      |  |
| 4. Title of the invention  | Process  |   |  |
| 5. Name of your agent (if you have one)  | Frank B. Dehn & Co.  |   |  |
| "Address for service" in the United Kingdom<br>to which all correspondence should be sent<br>(including the postcode)  | 179 Queen Victoria Street<br>London<br>EC4V 4EL                  |   |  |
| Patents ADP number (if you know it)  | 166001   |   |  |
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| 8. Is a statement of inventorship and of right<br>to grant of a patent required in support of<br>this request? (Answer 'Yes' if:<br>a) any applicant named in part 3 is not an inventor, or<br>b) there is an inventor who is not named as an<br>applicant, or<br>c) any named applicant is a corporate body.<br>See note (d)) | Yes  |   |  |

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Description

16

Claim(s)

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Abstract

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Drawing(s)

5

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

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Any other documents (please specify)

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11.

I/We request the grant of a patent on the basis of this application.

Signature

Frank B Dehn & Co

Date 13th November 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

Julian Cockbain

0171 206 0600

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Process

5           This invention relates to a process for the manufacture of an orally administrable pharmaceutical composition containing a physiologically tolerable calcium compound, in particular a composition in tablet form.

10           Calcium carbonate tablets are used as a source of calcium, especially for patients suffering from or at risk of osteoporosis. Moreover calcium carbonate is used as an acid neutralizing agent in antacid tablets.

15           Calcium carbonate is used in such tablets since the calcium content of calcium carbonate is high, the calcium is presented in a form which can be taken up from the gastrointestinal tract, calcium carbonate is effective at neutralizing gastric acids, and calcium carbonate is a physiologically acceptable calcium  
20           compound.

          In such tablets, various binders, sweeteners and flavors are used in order to produce a tablet which is readily acceptable to the patient. Indeed many producers have sought to achieve improved patient  
25           acceptability by formulating the tablets with such excipients in a "chewable" form. As a result, and since the daily recommended dosage is generally about 1000 mg calcium, the commercially available calcium tablets which commonly contain 500 mg calcium are relatively  
30           bulky.

          Examples of chewable calcium carbonate tablets are described in WO 96/09036 (Laboratoire Innothera) and in US-A-4446135 (Sterling Drug). The chewable calcium carbonate tablets described in these two patent  
35           publications have a calcium carbonate content of about 50% or less by weight and for a 500 mg calcium dosage are therefore undesirably large.

The present invention is directed to a process by which this undesired bulk may be reduced, and in particular to a process by which a chewable calcium tablet may be produced with a calcium compound content in excess of 60% by weight.

Thus viewed from one aspect the present invention provides a process for the preparation of an orally administrable calcium composition, said process comprising the steps of:

(i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a specific surface area of 0.1 to 1.2 m<sup>2</sup>/g, preferably 0.2 to 0.9 m<sup>2</sup>/g, especially 0.3 to 0.8 m<sup>2</sup>/g;

(ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate;

(iii) optionally mixing said first granulate with one or more further components to produce a second granulate, preferably a granulate having a content of said calcium compound of at least 60% by weight; and

(iv) optionally compressing said first or second granulate to form tablets.

The physical characteristics of the calcium compound used in the process of the invention are important in order that the fluid bed granulation stage should produce a first granulate having the desired characteristics. The calcium compound should be crystalline and have a mean particle size of 3 to 40 $\mu$ m, preferably 5 to 30 $\mu$ m. Preferably it should have a bulk density in the range of 0.2 to 1.5g/mL, more preferably 0.3 to 1.4g/mL, especially 0.4 to 1.3g/mL. The calcium compound is preferably an acid soluble compound, e.g. a compound poorly soluble or insoluble in water at pH7 but soluble in water at gastric pH values.



The upper particle size limit of  $40\mu\text{m}$  is important in order to avoid a gritty mouthfeel in the final product. The lower particle size limit of  $3\mu\text{m}$  is also important in order to avoid a feeling of stickiness on the teeth during chewing.

Crystallinity, in particular the possession of relatively smooth crystal surfaces and low specific surface area, is important for the achievement of effective and rapid wetting and granulation in the fluid granulation step of the process of the invention.

Specific surface area may be determined using apparatus such as the Carlo Erba Sorptomatic 1900.

The calcium compound may, for example, be selected from calcium carbonate, calcium lactate, calcium gluconate, calcium citrate, calcium glycerophosphate, calcium phosphate, calcium hydrogen phosphate (e.g. in tribasic, dibasic or monobasic forms, i.e.  $\text{Ca}_3(\text{PO}_4)_2$ ,  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$  and  $\text{Ca}(\text{HPO}_4)_2 \cdot \text{H}_2\text{O}$ ), calcium glucuronate, calcium aspartate, calcium glucoheptonate and mixtures of two or more thereof. However, calcium carbonate, in particular in calcite form, is preferred due to its high calcium content, its ready availability, its cost, its well-documented absorption characteristics in humans, and its performance in the fluid granulation step of the process of the invention.

Especially, preferably calcium carbonate having individual or primary and cubic or pseudo-cubic shaped calcite crystals with smooth or even surfaces are used. Desirably such crystals are also transparent. Where the end product is for use as a medicine, it is also preferred that the calcium carbonate be a material precipitated according to Ph. Eur.

Examples of appropriate commercially available calcium carbonate include Merck 2064 (available from Merck, Darmstadt, Germany), Scoralite 1A and Scoralite 1B (available from Scora Watrigant SA, France), Super-Purity  $\text{CaCO}_3$  and Medicinal Heavy  $\text{CaCO}_3$  (available from

Shanghai Da Yu Biochemistry Co. Ltd., China), and  
Pharmacarb LL (available from Crompton & Knowles,  
Vineland, USA). Scoralite 1B is particularly preferred.  
Merck 2064 has a mean particle size of 10 to 30 $\mu$ m, an  
5 apparent bulk density of 0.4 to 0.7 g/mL, and a specific  
surface area of 0.3 m<sup>2</sup>/g; Scoralite 1A has a mean  
particle size of 5 to 20 $\mu$ m, an apparent bulk density of  
0.7 to 1.0g/mL and a specific surface area of 0.6 m<sup>2</sup>/g;  
Scoralite 1B has a mean particle size of 10 to 30 $\mu$ m, an  
10 apparent bulk density of 0.9 to 1.2 g/mL and a specific  
surface area of 0.4 m<sup>2</sup>/g; Medicinal Heavy CaCO<sub>3</sub> has a  
mean particle size of 5 to 30  $\mu$ m, an apparent bulk  
density of 0.9 to 1.3 g/mL and a specific surface area  
of 0.8 m<sup>2</sup>/g; Super-Purity CaCO<sub>3</sub> has a mean particle size  
15 of 10 to 30  $\mu$ m, an apparent bulk density of 0.9 to 1.2  
g/mL and a specific surface area of 0.6 m<sup>2</sup>/g; and  
Pharmacarb LL has a mean particle size of 5 to 30  $\mu$ m, an  
apparent bulk density of 0.8 to 1.2 g/mL and a specific  
surface area of 0.7 m<sup>2</sup>/g. The Pharmacarb LL calcium  
20 carbonate however is not apparently a material  
precipitated in accordance with Ph. Eur. and thus is  
more preferred for production of end products which are  
for use as dietary supplements or food products than  
those which are for use as pharmaceuticals.

25 The calcium compound or mixture of calcium compound  
preferably makes up 60 to 95% by weight of the second  
granulate, and preferably provides a calcium content of  
15 to 40%, more especially 20 to 35%, and still more  
especially 25 to 30% by weight in the second granulate.

30 The calcium compound or mixture of compounds  
preferably makes up 60.5 to 96%, more preferably 66 to  
91% still more preferably 68 to 80% and most and most  
preferably 72 to 76% by weight of the first granulate.

The water-soluble diluent used in step (ii) of the  
35 process of the invention is preferably a sweetener or a  
mixture of sweeteners, e.g. a polyol or a  
polysaccharide, more preferably a non-cariogenic

sweetener. Examples of suitable diluents include sorbitol, xylitol and mannitol, which are non-cariogenic. Neosorb P100T sorbitol and xylitol CM50 are available commercially from Roquette Freres and Xyrofin respectively. The diluent preferably makes up the major proportion, e.g. by 70 to 96%, more preferably 80 to 95%, still more preferably 85 to 94%, most preferably 90 to 92% of the total weight of diluent and binder in the first granulate.

The calcium compound and diluent are preferably blended before addition of the aqueous binder. The blending may conveniently be performed as a dry blending, for example using a blender with a rotating mixer arm, e.g. a blade. This ensures that any lumps are removed and achieves an intimate mixing of the calcium compound and the diluent. By way of example, a high speed mixer (e.g. Fielder PMA 25/2G) may be used operating at maximum speed for both the impeller and knife for two minutes; however any mill may be used to break up lumps in the mixture and indeed the calcium compound and the diluent may be treated in this way separately to remove lumps before they are blended.

The water-soluble binder used in step (ii) of the process of the invention may be selected from known water-soluble pharmaceutical binders, e.g. it may be a soluble cellulose or polysaccharide or a polyvinylpyrrolidone or a mixture thereof. Preferably the binder is a polyvinylpyrrolidone, e.g. Kollidon K30 or Kollidon VA64 which are available commercially from BASF.

The binder is preferably used in aqueous solution at a concentration of 15 to 35% by weight, more especially 25 to 30%, particularly 27 to 29% by weight.

The fluid granulation step, step (ii) of the process of the invention, may be effected in any fluid granulation apparatus, e.g. a Glatt GPCG 3 fluid bed available from Glatt GmbH. The procedure preferably

involves spraying the aqueous binder mixture onto the fluidized diluent/calcium compound mixture.

Fluidization may be achieved by gas flow through the mixture or alternatively mechanically, e.g. by the use of counter-rotating, interlocking paddles with horizontal rotational axes. The liquid sprayed is preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C) and the particulate onto which it is sprayed is again preferably at or near ambient temperature (e.g. 15 to 35°C, preferably 20 to 30°C, more preferably about 25°C). The gas pressure of the spray chamber is conveniently ambient (e.g. 1 atmosphere). The spray rate may be adjusted, according to batch size and component identities and concentrations, to optimize the mean particle size of the first granulate. However, for a 3kg solids batch, a spray rate of 30 to 50g/min may be appropriate and a spray rate of about 40g/min is particularly preferred.

The granulate may be dried in a separate drier but preferably is dried in place in the fluidized bed mixer, e.g. using a heated gas (e.g. air) flow through the granulate. This can be effected while spraying of the binder solution is taking place or after spraying of the binder solution has been completed. Preferably a drying gas temperature of 60 to 90°C, more especially 65 to 75°C, in particular about 70°C is used. Particularly preferably drying is effected such that the granulate temperature reaches 40 to 50°C, especially about 43 to 45°C.

In this way a first granulate having a low water content, e.g. 1 to 5% by weight, preferably about 3%, may be produced and subsequently dried to a moisture content of about 0.1 to 0.5%, preferably 0.2% by weight, within an overall granulation and drying period of 15 to 45 mins, preferably 20 to 30 mins.

The first granulate preferably has a particle size

distribution (as determined by Malvern particle size analysis) as follows:

D (v, 0.1) = 15-21  $\mu\text{m}$

D (v, 0.5) = 70-120  $\mu\text{m}$

5 D (v, 0.9) = 190-330  $\mu\text{m}$

Where the first granulate is to be mixed with further components before tabletting, such further components will typically be one or more of the following: further active agents, e.g. vitamins, in  
10 particularly vitamin D, especially vitamin D<sub>3</sub>; effervescing agents; diluents; sweeteners; flavors; and lubricants, e.g. hydrogenated fatty acids, polyethyleneglycol, sodium stearyl fumarate, stearic acid and salts thereof, for example magnesium stearate.  
15 When a further active agent is added, this should be at a therapeutically effective dosage. When vitamin D is added, e.g. to produce a product suitable for treatment or prophylaxis of osteoporosis, this preferably is at a calcium to vitamin D ratio of 100 mg Ca: 30 to 150 IU  
20 Vitamin D, especially 100:35 to 100, more especially 100:40 to 90. Preferably the second granulate should be such as to be tablettable to produce tablets containing 500mg Ca and 200 to 250 IU or 400 to 450 IU vitamin D<sub>3</sub>.

Where vitamin D is used, this may conveniently be  
25 vitamin D<sub>2</sub> (ergocalciferol) or more preferably vitamin D<sub>3</sub> (cholecalciferol). Dose units of the second granulate, e.g. tablets formed therefrom, preferably contain 250 to 1500mg Ca and 5 to 30 $\mu\text{g}$  vitamin D.

Vitamin D<sub>3</sub> is commercially available from Roche in a  
30 granular form which consists of vitamin D<sub>3</sub> in edible fats finely dispersed in a starch coated matrix of gelatin and sucrose with D,L- $\alpha$ -tocopherol added as an antioxidant. However, other dry powder or granulate forms of vitamin D may also be used.

35 A chewable tablet containing 500 mg calcium and 5  $\mu\text{g}$  vitamin D<sub>3</sub> only contains 2.2 mg of the commercial quality of vitamin D<sub>3</sub> from Roche (100 CWS). This

constitutes only 0.13% of the total weight of the tablet and one may thus anticipate problems with the homogeneity of vitamin D<sub>3</sub> in the tablet. A Malvern particle size analysis of the 100 CWS quality typically gives the following results for the particle size distribution: D(v, 0.1)=180-250  $\mu$ m, D(v, 0.5)=240-300  $\mu$ m and D(v, 0.9)=320-400  $\mu$ m. It has been found desirable to sieve the vitamin D<sub>3</sub> on 60 mesh with a Russell vibrating sieve. This procedure will increase the number of vitamin D<sub>3</sub> particles per tablet and thus facilitate a more even and uniform distribution. In addition to this the sieving procedure will also eliminate all the coarse particles in the vitamin D<sub>3</sub> which also contribute to an inhomogeneous distribution.

Twenty consecutive batches of a chewable tablet containing 500 mg calcium and 5  $\mu$ g vitamin D<sub>3</sub> have been produced which have utilized a sieved (< 60 mesh) vitamin D<sub>3</sub> with a mean particle size in the region of 203-217  $\mu$ m. All twenty batches comply with the requirements set in the European Pharmacopeia with respect to the uniformity of content of vitamin D<sub>3</sub> in the tablet.

Where an active component is used which forms a minor part of the overall granulate, e.g. vitamin D, it is general preferred to produce a premix of such a component and the first granulate before mixing the premix and the remaining required quantity of the first granulate. This ensures uniform distribution of the minor component in the second granulate.

The second granulate also preferably contains a flavor, e.g. a fruit flavor, in particular a lemon or orange flavor, in order to mask the chalky taste of calcium carbonate. The flavor may, for example, be a lemon or orange oil dispersed in a hydrogenated glucose syrup material or, alternatively, it may be any other stable flavor, e.g. one of the Durarome flavors available from Firmenich.

Extra sweeteners, e.g. artificial sweeteners such as aspartame, acesulfame K, saccharin, sodium saccharin and sodium cyclamate may be used to enhance the sweetness of the granulate.

5        Such extra components may be mixed in during the fluid granulation step of the process of the invention, but preferably they are mixed in with the first granulate in a separate dry mixing step, optionally after a sieving step to ensure homogeneous mixing.

10        When the granulate is to be tabletted, it preferably includes a lubricant, e.g. magnesium stearate, stearic acid, hydrogenated fatty acids, sodium stearyl fumarate, PEG 6000 or PEG 8000. Magnesium stearate is generally preferred. Such a lubricant will  
15        generally make up 0.3 to 1.5%, particularly 0.35 to 1.0% by weight of the composition to be tabletted. The lubricant is preferably added in a final mixing step and mixed in for a brief time to prevent overmixing and subsequent lack of cohesion in the tabletted product.

20        Where the granulate is to be tabletted, this can be effected on conventional tablet presses. Preferably the tablet so produced will have a total weight of 500 to 3000mg, more especially 1000 to 2500mg, most preferably 1500 to 2000mg. If desired however, the granulate  
25        (either the first granulate or the second granulate) may be used for other administration forms, e.g. powders, capsules, lozenges, coated tablets, etc. In general dose units (e.g. tablets or sachet contents) will contain 100 to 1000 mg Ca, especially 250 to 750 mg Ca,  
30        most preferably 450 to 550 mg Ca. The granulate is itself novel and forms a further aspect of the invention. Viewed from this aspect, the invention provides a granulate, preferably a tablettable granulate, comprising a fluid bed granulation granulate  
35        product of a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the

range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g.

5 The present invention makes it possible to reduce the amount of soluble diluent and binder in a chewable calcium tablet while sustaining the desirable chewability by the production of a highly porous granulate by fluid bed granulation using a calcium compound with a relatively high degree of crystallinity and with smooth faces to the crystals. This high degree  
10 of porosity, desirably 20 to 30%, results in the final chewable tablet having improved sensoric properties despite having a high calcium content. Such properties include improved dispersion in water and reduced stickiness during mastication.

15 The porosity of the granulate or tablet may be determined using mercury intrusion porosimetry (e.g. using a Carlo Erba Porosimeter 2000), and by helium adsorption, e.g. using an AccuPyc 1330 pycnometer to measure true density and a Geopyc 1360 envelope  
20 measuring apparatus. AccuPyc 1330 and Geopyc 1360 apparatus are available from Micrometrics. Mercury intrusion porosimetry is the more suitable of the two techniques for measuring the porosity of a granulate while both techniques can be used for measuring the  
25 porosity of a tablet.

The invention will now be described further with reference to the following non-limiting Examples and the accompanying drawings in which Figures 1 to 6 are  
30 scanning electron micrographs of six different grades of calcium carbonate and Figures 7A, 7B, 8A and 8B are scanning electron micrographs of granulates prepared according to the invention at lower (Figs. 7A and 8A) and higher (Figs. 7B and 8B) magnification:



EXAMPLE 1

Preparation of First Granulate

5 A binder solution is prepared containing 27.7% by weight of polyvinylpyrrolidone (Kollidon K30) in purified water. This is temperature-controlled at 20°C before spraying.

10 A batch of 74.5 parts by weight calcium carbonate (Scoralite 1B) and 23.3 parts by weight sorbitol (Neosorb P100T) is blended for two minutes using a high speed mixer (Fielder PMA 25/2G) set at maximum mixing speed. 3.0kg of this blend are then placed at 23-26°C in the mixer chamber of a Glatt GPCG3 fluid bed mixer.

15 The polyvinylpyrrolidone solution is then sprayed onto the fluidized blend at a rate of 40g/min until a total of 280g of liquid has been added. Spraying is effected into air at an inlet temperature of 45°C and at ambient pressure.

20 Air at 70°C is then passed through the sprayed granulate until it is dry (about 0.2% by weight residual moisture content). At this stage, the granulate temperature is about 44°C. The total duration of the spraying and drying stage is about 25 minutes.

25 At the end of the drying stage the first granulate has the following properties:

mean particle size distribution  $D(v, 0.1) = 16 \mu\text{m}$ ,  $D(v, 0.5) = 100 \mu\text{m}$ , and  $D(v, 0.9) = 284 \mu\text{m}$

Bulk density: 0.73g/mL

Porosity: 20-30%

30 Flowability (Carrs index %) : 13

The mean particle size analysis is performed on a Malvern Mastersizer S long bench apparatus  $D(v, 0.1)$ ,  $D(v, 0.5)$ , and  $D(v, 0.9)$  give the particle sizes for which 10%, 50% and 90% of the particles by volume have sizes  
35 below the given values.

EXAMPLE 2

Preparation and Tableting of Second Granulate

5 4.4 parts by weight of sieved (< 60 mesh) Vitamin D<sub>3</sub> from Roche and 32 parts by weight of the first granulate are dry mixed in a twin cone convection blender to form a pre-mix.

10 The pre-mix, the first granulate, lemon flavour granulate and aspartame are then dry mixed in a conical screw mixer to produce a granulate which is then mixed for 9 minutes. Magnesium stearate is added and mixed for an additional 3 minutes to produce a second granulate comprising:

|    |  |                      |
|----|--|----------------------|
| 15 | Calcium carbonate  | 1250 parts by weight |
|    | Sorbitol   | 390 parts by weight  |
|    | Polyvinylpyrrolidone                                       | 36.4 parts by weight |
|    | Vitamin D <sub>3</sub> 100 000 IU/g<br>(100CWS from Roche) | 4.4 parts by weight  |
| 20 | Lemon flavour<br>(in dehydrated glucose syrup)             | 50.7 parts by weight |
|    | Aspartame  | 1 part by weight     |
|    | Magnesium stearate   | 6 part by weight     |

25 This mixture is then tabletted to produce biconvex tablets of 16mm diameter containing 1250 mg calcium carbonate.

30 The characteristics of the tablets are as follows:  
**Breaking strength:** The chewable tablet has a normal biconvex shape and a diameter of 16 mm. The tablet initially has a breaking strength of 6 to 7.5 kp which can increase to approximately 8 to 9 kp after 24 hour storage. This breaking strength gives a satisfactory chewability and at the same time resistance towards handling and packaging into tablet bottles.

35 The breaking strength values may however vary between 4.5 to 8.0 kp according to the size of the tablet (12-21 mm).

**Friability:** A breaking strength of 6 to 7.5 kp for a chewable tablet with a diameter of 16mm results in friability values of less than 1%. This low value for the friability ensures sufficient firmness with respect to handling and packaging.

**Disintegration:** A characteristic feature of this chewable tablet formulation is the very fast disintegrating time.

The disintegration time is typically between 3 and 6 min. It is also a characteristic feature of the tablet that it disintegrates into the primary crystals of calcium carbonate which ensures a rapid exposure of calcium carbonate for dissolution.

This is important for the in vivo dissolution of calcium carbonate in the acidic gastric medium in the stomach and the subsequent absorption of calcium in the gastrointestinal tract.

**Porosity:** The tablet has a characteristic porosity of 25-30%. The porosity is determined by both mercury intrusion porosimetry and helium adsorption as described above. Both techniques gave porosity values in the range 25-30% for the tablet.

**Dissolution:** The dissolution rate is typically quick with 90% elemental calcium being dissolved within 10 min in 900 ml of 0.1 N HCl at 37°C (Ph. Eur., rotating paddle at 50 RPM).

### EXAMPLE 3

#### Lozenge to be sucked

Using a process analogous to that of Examples 1 and 2 lozenges are prepared with the following composition:

Calcium granulate:

|                                       |          |
|---------------------------------------|----------|
| Calcium carbonate (Scoralite 1B):     | 1250 mg  |
| Xylitol (CM50):                       | 390 mg   |
| Polyvinylpyrrolidone (Kollidon K 30): | 36.40 mg |

|   |   |         |
|---|---|---------|
|   | Vitamin D <sub>3</sub> 100 000 IU/g (100 CWS from Roche): | 4.4 mg  |
|   | Lemon flavor:   | 50.7 mg |
|   | Anhydrous citric acid:                                    | 8.0 mg  |
|   | Aspartame:  | 1.0 mg  |
| 5 | Magnesium stearate:                                       | 6.0 mg  |
|   |   | <hr/>   |
|   | Sum tablet weight:  | 1747 mg |
|   |   | <hr/>   |

10 EXAMPLE 4

Sachet product to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 2 but with sorbitol replaced by anhydrous citric acid, sachets are prepared with the following granulate  
15 contents:

|    |   |                |
|----|---|----------------|
|    | Calcium granulate:  |                |
|    | Calcium carbonate (Scoralite 1A):                         | 1250 mg        |
|    | Citric acid, anhydrous                                    |                |
| 20 | (powder quality)  | 2150 mg        |
|    | Polyvinylpyrrolidone (Kollidon VA 64):                    | 36.60 mg       |
|    | Vitamin D <sub>3</sub> 100 000 IU/g (100 CWS from Roche): | 4.4 mg         |
|    | Lemon flavor:   | 300 mg         |
|    | Aspartame:  | 15.0 mg        |
| 25 | Acesulfam K:  | <u>14.0 mg</u> |
|    | Sum sachet contents weight:                               | 3770 mg        |
|    |   | <hr/>          |

EXAMPLE 5

30 Granulate to be dispensed from a granulate dispensing unit

This product may be used as a food additive or as a functional food where the consumer takes a dosage  
35 equivalent to 500-1000 mg of elemental calcium and uses this as a supplement in daily food products, such as for example breakfast cereals and fruit juices. The

granulate is produced by a process analogous to that of Examples 1 and 2 with the following composition:

Calcium granulate:

|   |  |                |
|---|--|----------------|
| 5 | Calcium carbonate (Scoralite 1A+1B):           | 1250 mg        |
|   | Xylitol (CM 50):                               | 390 mg         |
|   | Polyvinylpyrrolidone (Kollidon VA 64):         | <u>36 mg</u>   |
|   | Granulate weight per 500 mg Ca <sup>2+</sup> : | <u>1676 mg</u> |

10 EXAMPLE 6

Effervescent tablet to be dispersed in a glass of water

Using a process analogous to that of Examples 1 and 2, effervescent tablets are prepared with the following composition:

15

Calcium granulate:

|    |   |                |
|----|---|----------------|
|    | Calcium carbonate (Scoralite 1A+1B):                      | 1250 mg        |
|    | Citric acid, anhydrous<br>(powder quality)                | 2150 mg        |
| 20 | Polyvinylpyrrolidone (Kollidon VA 64):                    | 36.60 mg       |
|    | Vitamin D <sub>3</sub> 100 000 IU/g (100 CWS from Roche): | 4.4 mg         |
|    | Lemon flavor:   | 300 mg         |
|    | Aspartame:  | 15.0 mg        |
|    | Acesulfam K:  | 15.0 mg        |
| 25 | Sodium stearate fumarate:                                 | 19.0 mg        |
|    | Sum tablet weight:  | <u>3790 mg</u> |

30 EXAMPLE 7

Calcium carbonate grades

35 Samples of Scoralite 1B, Scoralite 1A, Super Purity CaCO<sub>3</sub>, Medicinal Heavy CaCO<sub>3</sub>, Pharmacarb LL and Merck 2064 were investigated using a scanning electron microscope (SEM). SEM pictures of these grades of

calcium carbonate are presented in Figures 1 to 6 respectively of the accompanying drawings.

Granulates made analogously to Example 1 using Scoralite 1B and Super Purity  $\text{CaCO}_3$  were also investigated by SEM and SEM pictures of these granulates at lower (A) and higher (B) magnifications are presented in Figures 7 and 8 of the accompanying drawings. The pictures of the two granulates clearly show their high degree of porosity, a property which is important for the fast disintegration/dissolution of tablets made therefrom. Moreover, this high degree of porosity is important for the sensory properties such as chewability and avoidance of sticking to the teeth during mastication.

Claims:

1. A process for the preparation of an orally administrable calcium composition, said process  
5 comprising the steps of:
  - (i) obtaining a physiologically tolerable particulate calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g;  
10
  - (ii) mixing said calcium compound with a water-soluble diluent and an aqueous solution of a water soluble binder in a fluid bed granulation apparatus and drying the resulting mixture to produce a first granulate;  
15
  - (iii) optionally mixing said first granulate with one or more further components to produce a second granulate, preferably a granulate having a content of said calcium compound of at least 60% by weight; and  
20
  - (iv) optionally compressing said first or second granulate to form tablets.
2. A granulate, preferably a tabletable granulate, comprising a fluid bed granulation granulate product of  
25 a physiologically tolerable calcium compound, a water-soluble binder and a water-soluble diluent, said calcium compound having a mean particle size in the range 3 to 40 $\mu$ m, having a crystalline structure and having a surface area of 0.1 to 1.2 m<sup>2</sup>/g.

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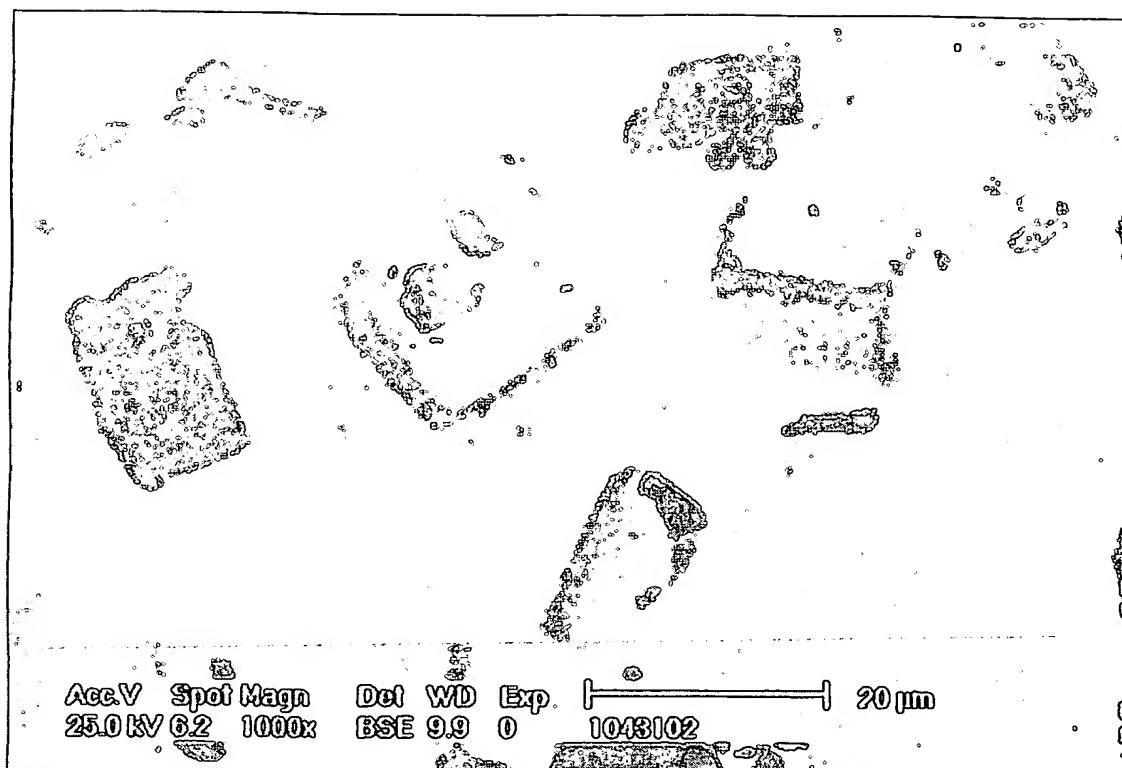


FIGURE 1

SCORALITE 1B

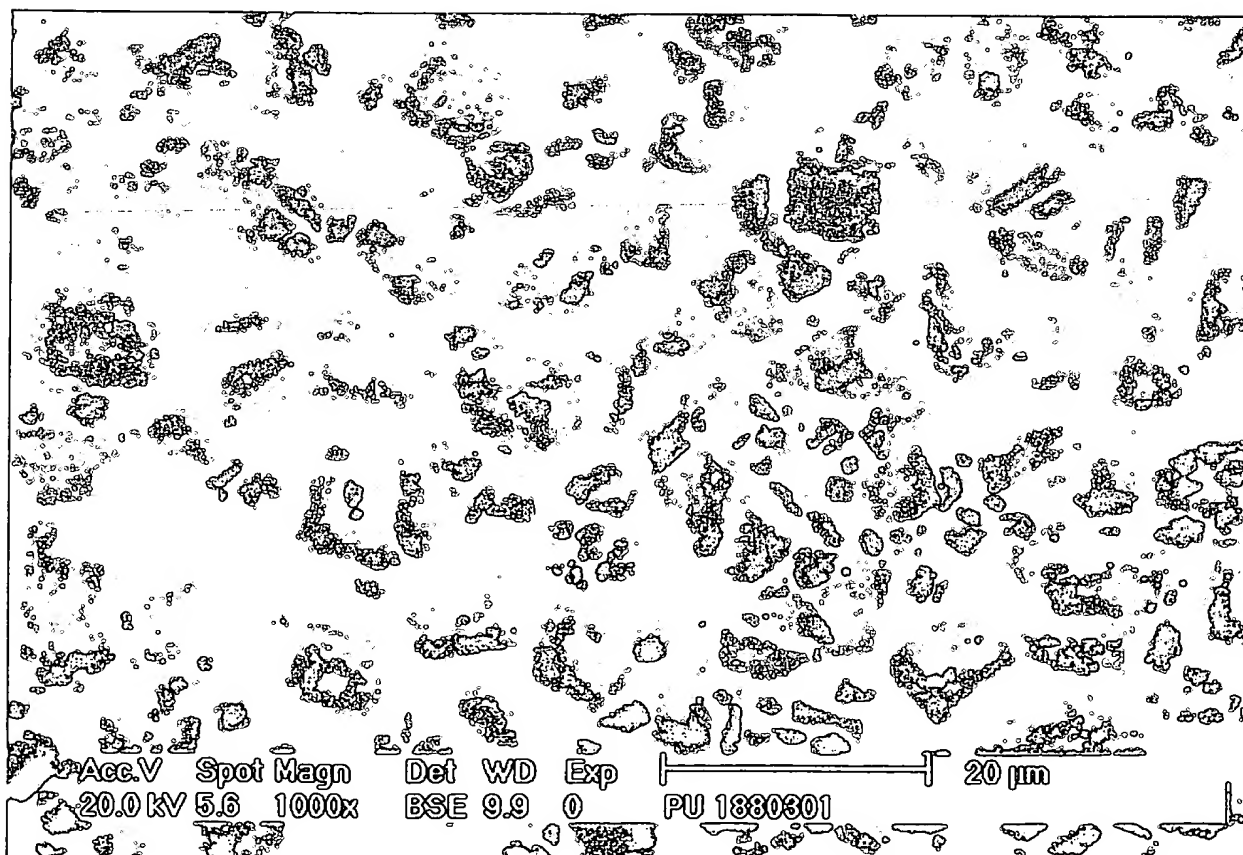


FIGURE 2

SCORALITE 1A

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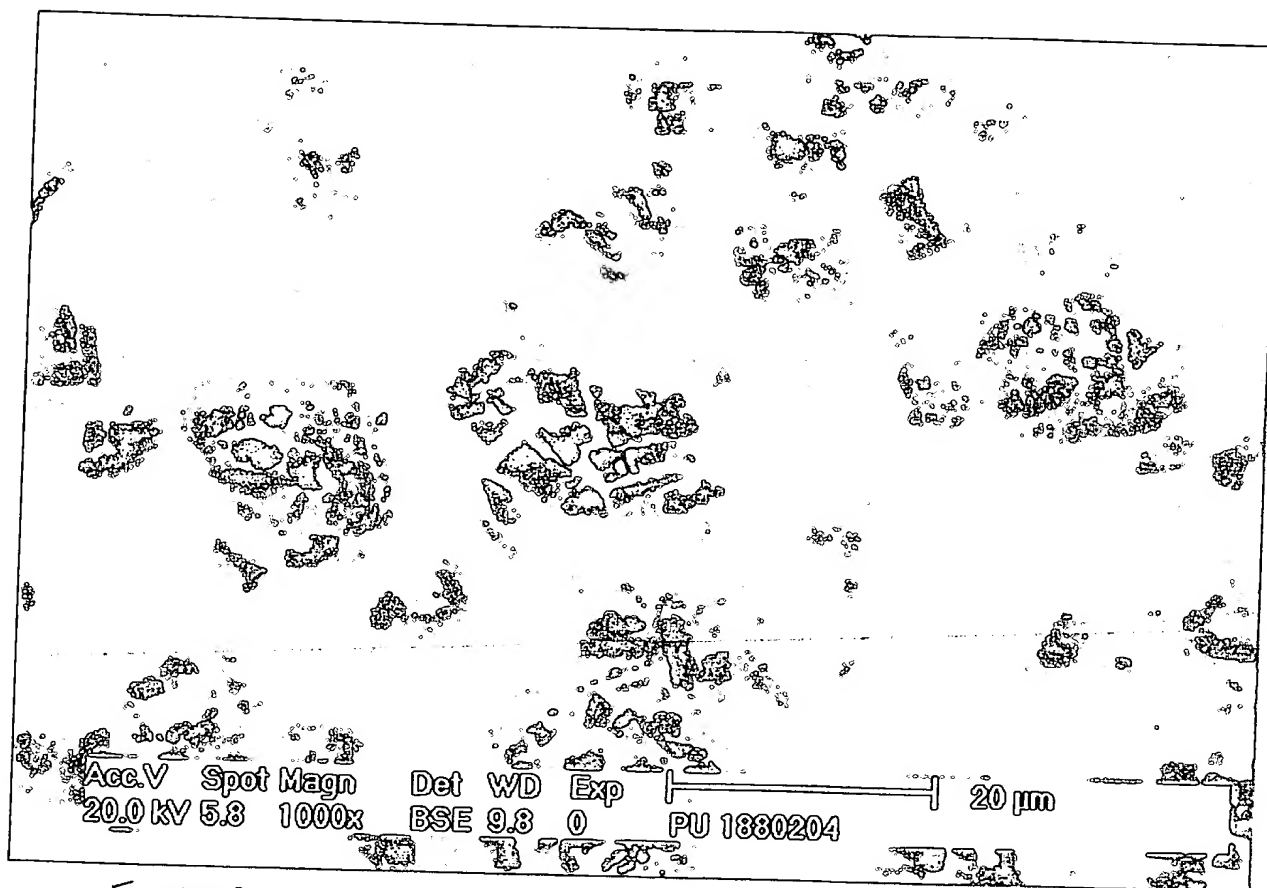


FIGURE 3

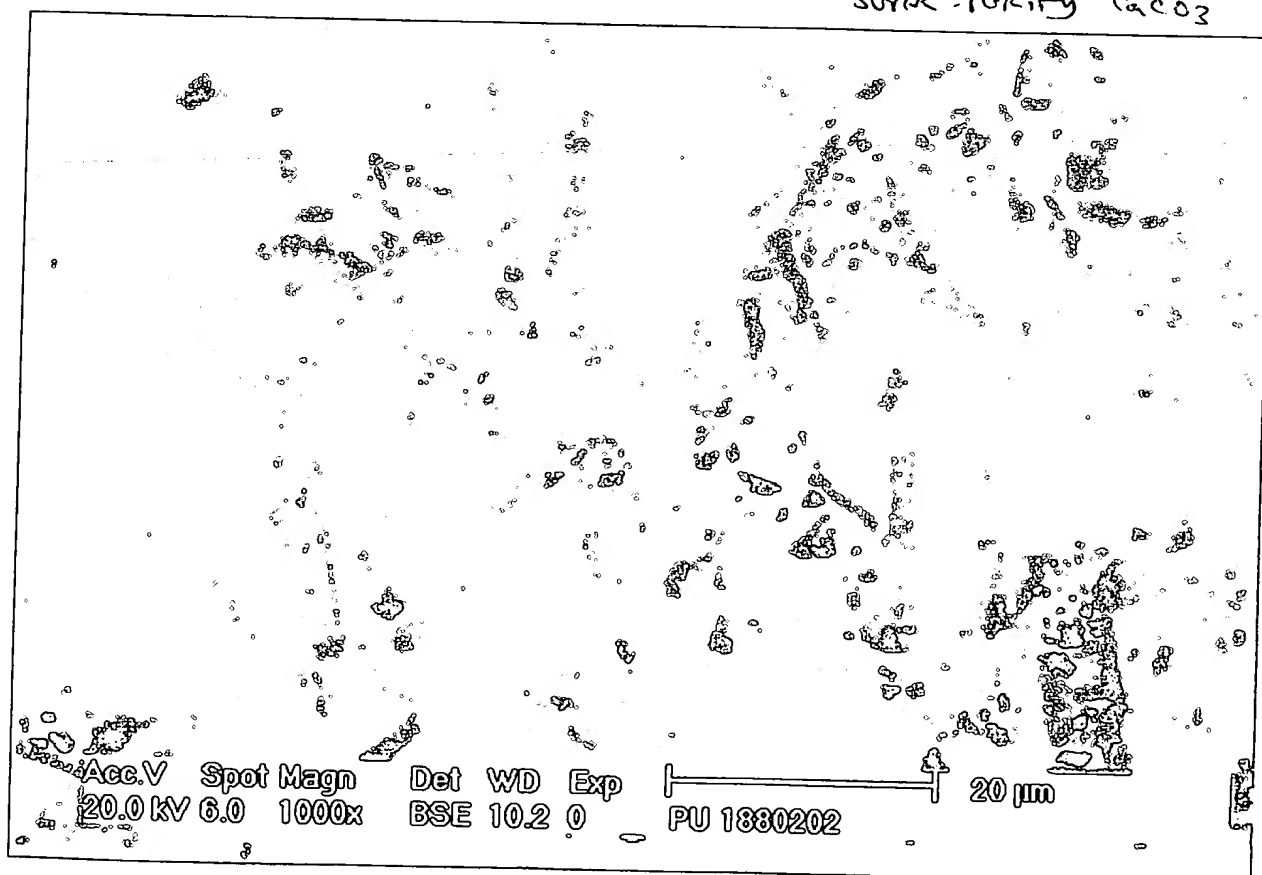
Super-Purity  $\text{CaCO}_3$ 

FIGURE 4

Medicinal Heavy  $\text{CaCO}_3$

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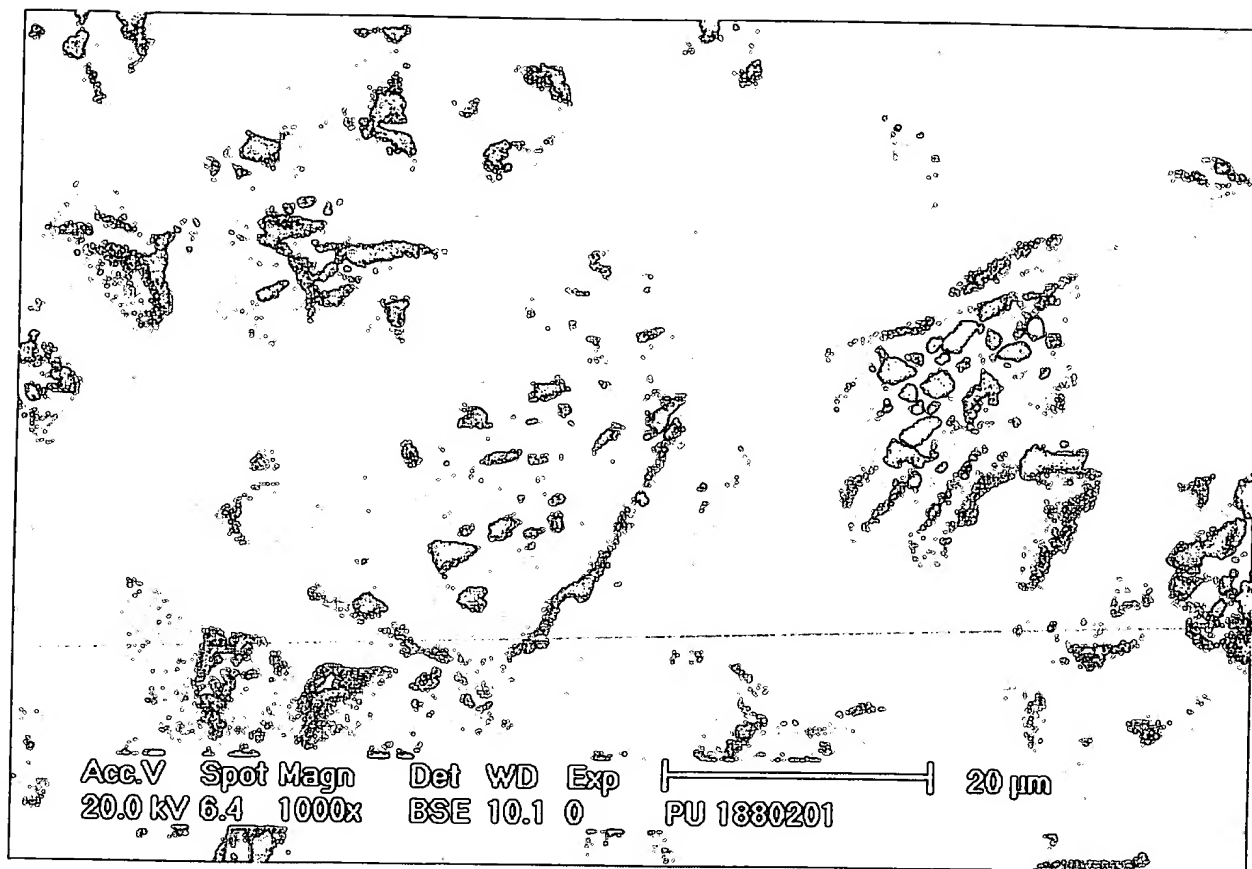


FIGURE 5

PHARMA CARB LL

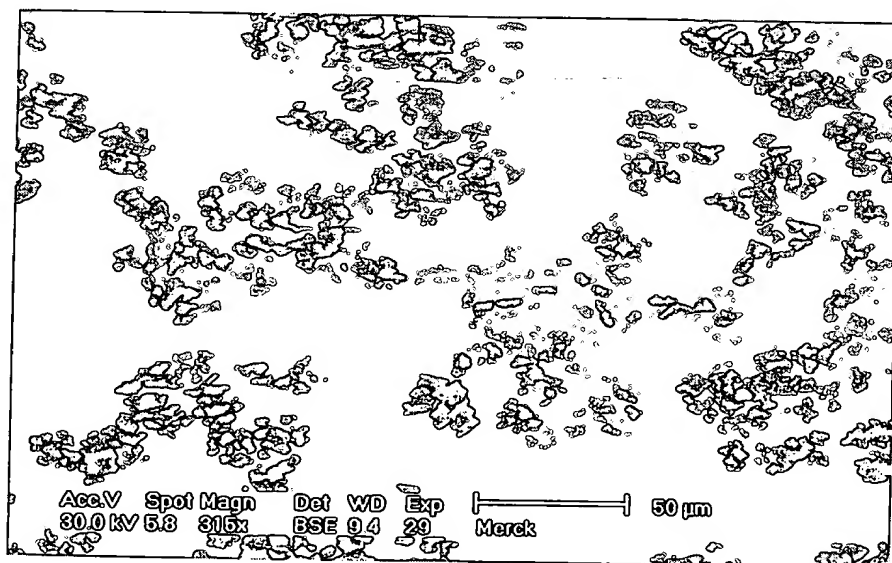


FIGURE 6

MERCK 2064

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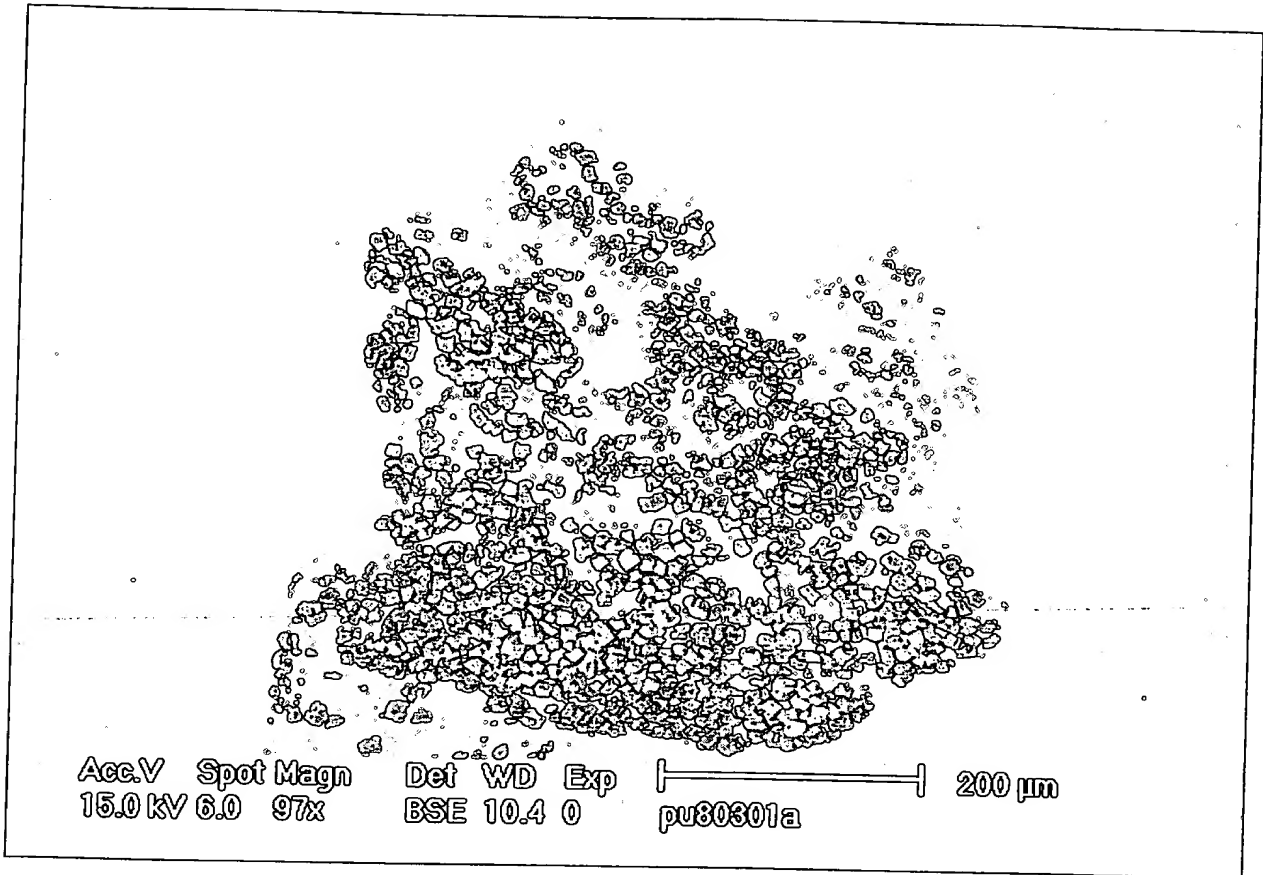


FIGURE 7A

SCORALITE 1B

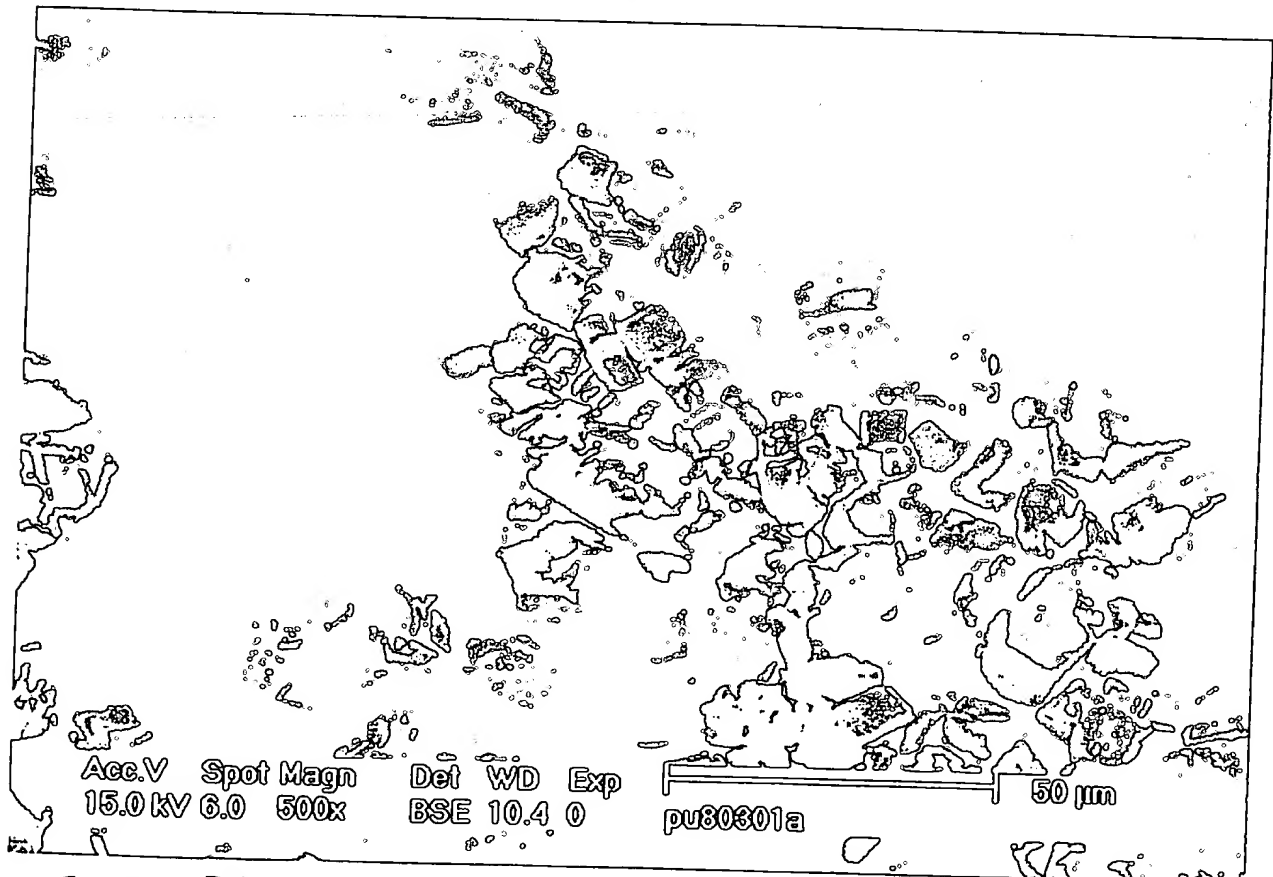


FIGURE 7B

SCORALITE 1B

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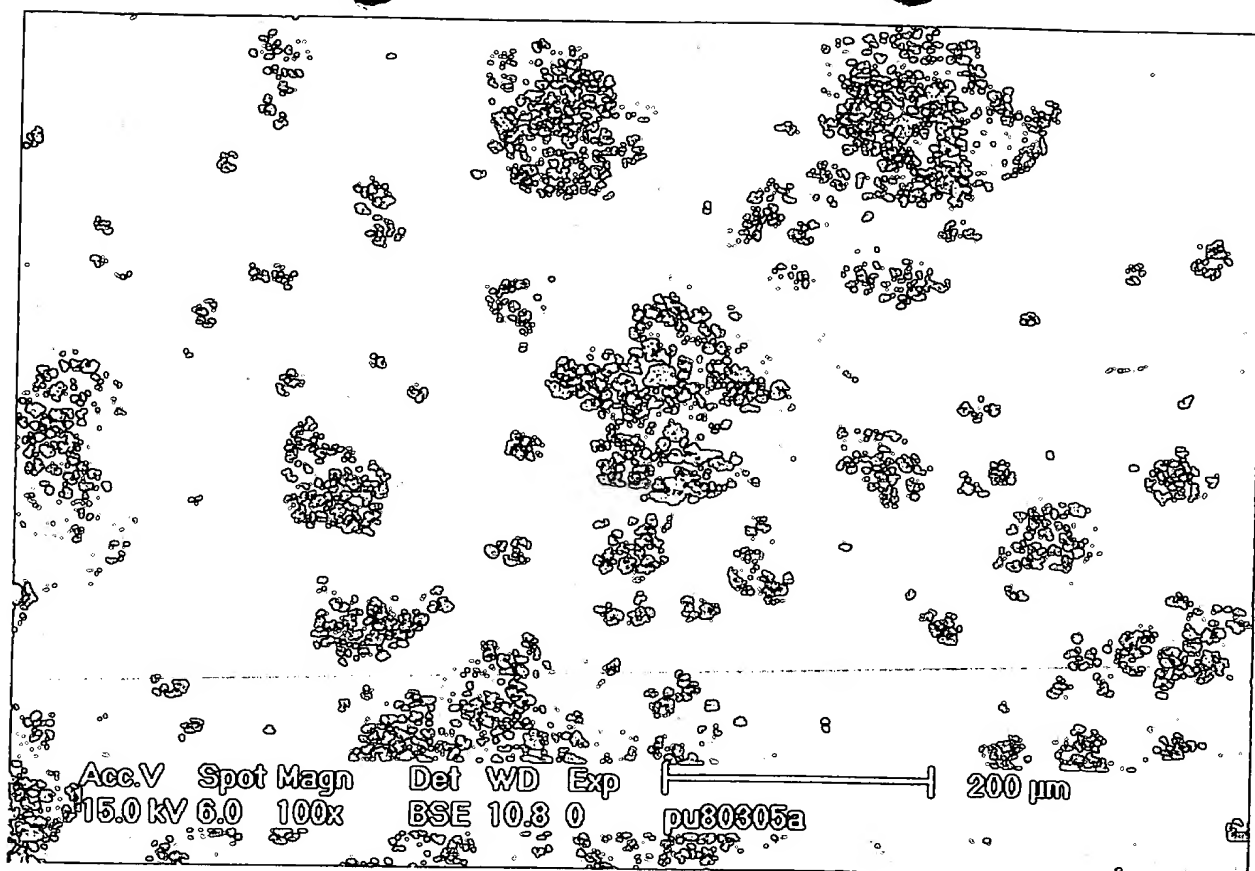


FIGURE 8A

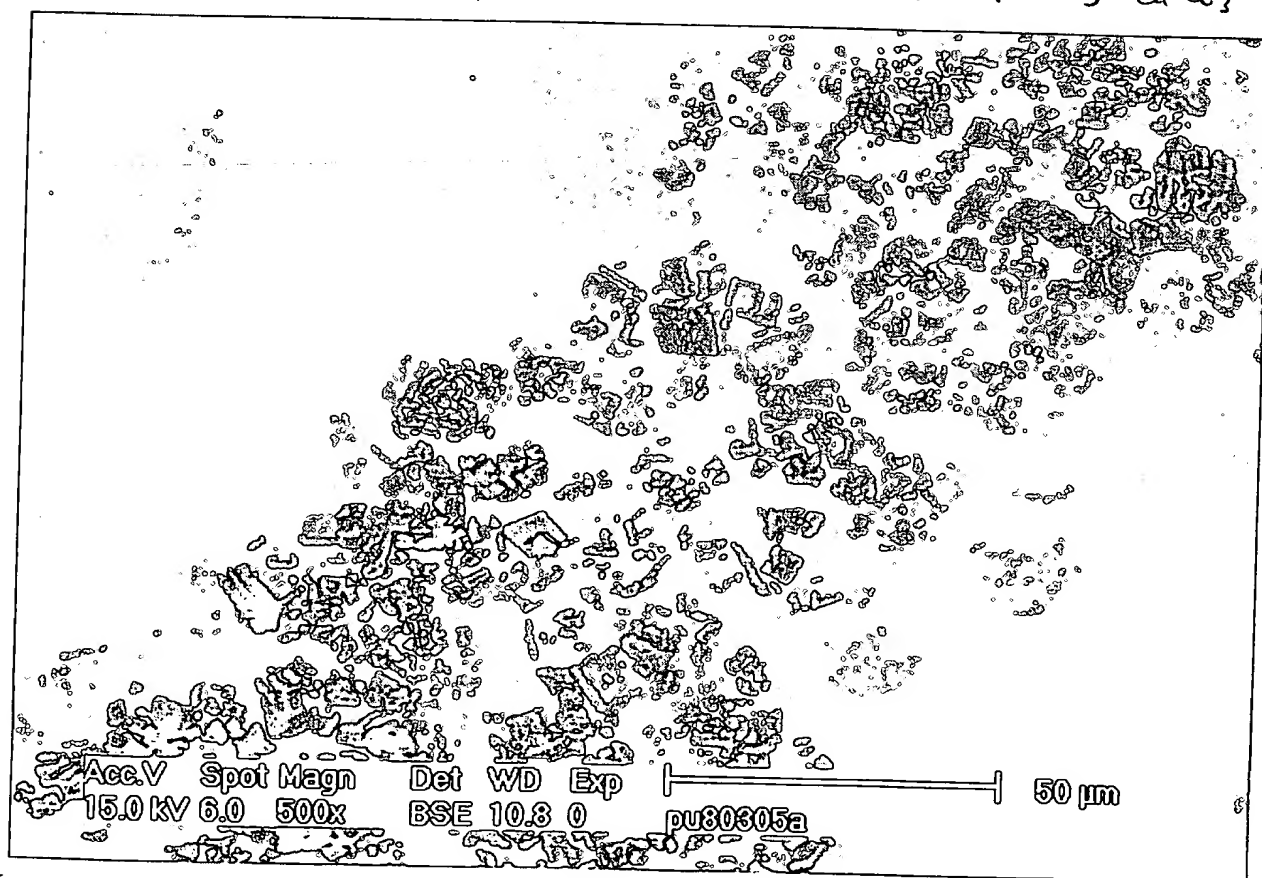
SUPER PURITY  $\text{CaCO}_3$ 

FIGURE 8B

SUPER PURITY  $\text{CaCO}_3$

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